## REMARKS

The Official Action of April 6, 2004 has been carefully considered and reconsideration of the application as amended is respectfully requested.

The courtesy of Examiner Jones in discussing this application with the undersigned on September 10, 2004 is gratefully acknowledged. The Interview Summary of 10 September 2004 accurately reflects what transpired as amplified below.

Claims 14 and 15 have been amended to remove the recitations that tied the amount of the compound of formula II in the claimed composition to the recited diseases. Claim 14 now recites that the compound of formula II is present in an amount that is effective to provide the composition with CRF antagonist activity in a patient to be treated in accordance with the disclosure at, for example, the Abstract (page 145) and page 48, third full paragraph. Claim 15 recites that the compound is present in an amount of between about 0.1 to about 50 mg/kg body weight of the patient to be treated in accordance with the disclosure at page 48, second full paragraph.

The amendments to claims 14 and 15 are respectfully believed to remove the bases for the Examiner's rejections under 35 USC 112, first paragraph, at paragraphs 11-14 of the Official Action since the Examiner has agreed with Applicant that there is support in the specification for the binding of the instantly claimed antagonists to CRF (see, e.g., paragraph 4 of the Official Action).

The comments of the Examiner at paragraphs 6-9 concerning the rejoinder of process claims that depend from or otherwise include all the limitations of product claim 1, once product claim 1 is found to be allowable, have been noted with appreciation. Applicants have now depended method claims 46-52 from product claim 1 for rejoinder of these claims once product claim 1 is found to be allowable. The recitations in these claims correspond to recitations in original claims 18-23.

Claims 1-3, 7, 11 and 12 have been amended to remove the bases for the rejections under 35 USC 112, second paragraph appearing at paragraphs 16-20 of the Official Action. The amendments correct informalities, and the informalities and the corrections would have been clear to a person of ordinary skill in the art from the application as filed. Claim 30 has been canceled whereby to render moot the basis for the rejection to this claim. All claims as amended are believed to be sufficiently definite to satisfy the dictates of 35 USC 112, second paragraph.

Claims 1-15 and 29-45 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-22 of copending Application No. 09/761,611. The Examiner has since clarified by telephone that the application number is in error and that the correct application number for this double patenting rejection is 09/761,995.

Applicants respectfully submit that an updated review of application serial number 09/761,995 shows that a double patenting rejection in view of this application

is inappropriate. This application as originally filed included claims directed to a compound structurally related to the subject matter of the instant application. However, application serial number 09/761,995 has now been allowed with only claims (copy submitted herewith) that are directed to a compound that is not related to the subject matter of the instant application. Accordingly, it is respectfully submitted that this double patenting rejection should now be withdrawn.

Claims 1-15 and 29-45 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-22 of copending Application No. 10/160,206. Applicant submits herewith a terminal disclaimer to overcome this rejection.

Claims 1-15 and 29-45 continue to be rejected under 35 USC 103(a) as allegedly being unpatentable over DE 3,145,287. Applicant respectfully traverses this rejection.

The Examiner has acknowledged that the claims differ from the prior art by having a double bond in lieu of a single bond of a pyrrolidinyl ring moiety of the prior art. The Examiner nevertheless argues that "although there is the issue of aromaticity in the prior art compound, the close structural relationship to the claimed compounds would be rendered obvious". It is respectfully submitted that this argument is a circular argument that begs the question: how can there be a sufficiently close structural relationship to predict similarity in properties in view of the aromaticity issue? The difference between a heteroaromatic ring and a non-aromatic ring is a very significant structural difference, as one of skill in the art would readily appreciate (see, e.g.,

Morrison and Boyd reference cited at page 20 of Applicant's Amendment dated December 5, 2003). Given this significant structural difference, it cannot be said that there is a sufficiently close structural relationship between the respective prior art and claimed compounds to predict a similarity in properties. Accordingly, and in the absence of any suggestion in the prior art for the proposed heteroaromatic to non-aromatic substitution, the cited art is respectfully not sufficient to set forth even a *prima facie* case of obviousness for the claimed invention (see *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985)).

In the interview, the Examiner made clear that he recognizes the significant differences between a heteroaromatic ring and a non-aromatic ring, and acknowledged that the prior art rejection is based solely on an alleged structural similarity between the claimed compound and the compounds described in the primary reference, DE 3145287. The undersigned pointed out that, under applicable authority, to establish a *prima facie* case of obviousness there must be a sufficiently close structural relationship to create an expectation that a claimed compound and a prior art compound would have similar properties (see MPEP Section 2144.09). Moreover, to establish such *prima facie* case, the USPTO has the burden to point to facts or to a chemical theory to support the position that a particular structural similarity between a claimed compound and a prior art compound would create such expectation. See, e.g., *In re Mills*, 126 USPQ 513, 517 (CCPA 1960) ("If the Patent Office wishes to rest a rejection on chemical theory, it is its duty to support its case with adequate evidence of the existence and meaning of that theory."); see, also, *In re Grabiak*, 226 USPQ 870, 872 (Fed. Cir. 1985) ("If evidence of

similar biological properties between -C(O)OR and -C(O)SR groups is to be relied upon, it must come from the prior art."). In view of the recognized differences between a heteroaromatic ring and a non-aromatic ring, Applicant submits that there would have been no motivation for one of skill in the art to make the claimed compound in the expectation that it would have similar properties to the prior art compound.

In view of the above, it is respectfully submitted that all objections and rejections of record have been overcome and that the application is now in allowable form. An early notice of allowance is earnestly solicited and is believed to be fully warranted.

Respectfully submitted,

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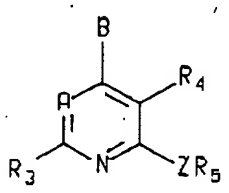
**Complete listing of claims:**

1. (Currently Amended) A compound of the formula



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or a pharmaceutically acceptable salt thereof, wherein

A is $-CR_7$;

B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_2R_{12})R_1$, $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_2OR_1$, $-CHR_1OR_2$, $-CHR_2SR_1$, ~~$-C(S)R_2$~~, ~~$-C(O)R_2$~~, $-CHR_2NR_1R_2$, $-CHR_1NHR_2$, $-CHR_1N(CH_3)R_2$, or $-NR_{12}NR_1R_2$;

Z is NH, O, S, $-N(C_1-C_2$ alkyl), $-NC(O)CF_3$, or $-C(R_{13}R_{14})$, wherein $R_{13}$ and $R_{14}$ are each, independently, hydrogen, trifluoromethyl or methyl, or one of $R_{13}$ and $R_{14}$ is cyano and the other is hydrogen or methyl, or $-C(R_{13}R_{14})$ is a cyclopropyl group, or Z is nitrogen or CH and forms a five or six membered heterocyclic ring fused with $R_5$, which ring optionally includes two or three further hetero members selected independently from oxygen, nitrogen, $NR_{12}$, and $S(O)_m$, and optionally includes from one to three double bonds, and is optionally substituted with halo, $C_1-C_4$ alkyl, $-O(C_1-C_4$ alkyl), $NH_2$, $NHCH_3$, $N(CH_3)_2$, $CF_3$, or $OCF_3$, with the proviso that said ring does not include any –S-S-, -S-O-, -N-S-, or –O-O- bonds, and does not include more than two oxygen or $S(O)_m$ heterologous members;

$R_1$ is C(O)H, $C(O)(C_1-C_6$ alkyl), $C(O)(C_1-C_6$ alkylene)$(C_3-C_8$ cycloalkyl), $C(O)(C_3-C_8$ cycloalkylene)$(C_3-C_8$ cycloalkyl), $C(O)(C_1-C_6$ alkylene)$(C_4-C_8$ heterocycloalkyl), $-C(O)(C_3-C_8$ cycloalkylene)$(C_4-C_8$ heterocycloalkyl), ~~$C_4-C_8$ alkyl,~~ $C_3-C_8$ cycloalkyl, $C_4-C_8$ heterocycloalkyl, $-(C_1-C_6$ alkylene)$(C_3-C_8$ cycloalkyl), $-(C_3-C_8$ cycloalkylene)$(C_3-C_8$ cycloalkyl), $-(C_1-C_6$ alkylene)$(C_4-C_8$ heterocycloalkyl), $-(C_3-C_8$ cycloalkylene)$(C_4-C_8$ heterocycloalkyl), or –O-aryl, or $-O-(C_1-C_6$ alkylene)-aryl; wherein said aryl, $C_4-C_8$ heterocycloalkyl, $C_1-C_6$ alkyl, $C_3-C_8$ cycloalkyl, $C_3-C_8$ cycloalkylene, and $C_1-C_6$ alkylene groups may each independently be optionally substituted with from one to six fluoro and may each independently be optionally substituted with one or two substituents $R_8$ independently selected from the group consisting of $C_1-C_4$ alkyl, $-C_3-C_8$ cycloalkyl, hydroxy, chloro, bromo, iodo, $CF_3$, $-O-(C_1-C_6$ alkyl), $-O-(C_3-C_5$ cycloalkyl), $-O-CO-(C_1-C_4$ alkyl), $-O-CO-NH(C_1-C_4$ alkyl), $-O-CO-N(R_{24})(R_{25})$, $-N(R_{24})(R_{25})$, $-S(C_1-C_4$ alkyl), $-S(C_3-C_5$ cycloalkyl), $-N(C_1-C_4$alkyl)$CO(C_1-C_4$ alkyl), $-NHCO(C_1-C_4$ alkyl), $-COO(C_1-C_4$ alkyl), $-CONH(C_1-C_4$ alkyl), $-CON(C_1-C_4$ alkyl)$(C_1-C_2$ alkyl), CN, $NO_2$, $-OSO_2(C_1-C_4$ alkyl), $S^+(C_1-C_6$ alkyl)$(C_1-C_2$ alkyl)$I^-$, $-SO(C_1-C_4$ alkyl) and $-SO_2(C_1-C_4$ alkyl); and wherein the $C_1-C_8$ alkyl, $C_1-C_6$ alkylene, $C_5-C_8$ cycloalkyl, $C_5-C_8$ cycloalkylene, and $C_5-C_8$

heterocycloalkyl moieties of $R_1$ may optionally independently include from one to three double or triple bonds; and wherein the $C_1$-$C_4$ alkyl moieties and $C_1$-$C_6$ alkyl moieties of $R_8$ can optionally independently be substituted with hydroxy, amino, $C_1$-$C_4$ alkyl, aryl, -$CH_2$-aryl, $C_3$-$C_5$ cycloalkyl, or –O-($C_1$-$C_4$ alkyl), and can optionally independently be substituted with from one to six fluoro, and can optionally include one or two double or triple bonds; and wherein each heterocycloalkyl group of $R_1$ includes from one to three heteromoieties selected from oxygen, $S(O)_m$, nitrogen, and $NR_{12}$;

$R_2$ is hydrogen, $C_1$-$C_{12}$ alkyl, $C_3$-$C_8$ cycloalkyl, $C_4$-$C_8$ heterocycloalkyl, -($C_1$-$C_8$ alkylene)($C_3$-$C_8$ cycloalkyl), -($C_3$-$C_8$ cycloalkylene)($C_3$-$C_8$ cycloalkyl), -($C_1$-$C_6$ alkylene)($C_4$-$C_8$ heterocycloalkyl), -($C_3$-$C_8$ cycloalkylene)($C_4$-$C_8$ heterocycloalkyl), aryl, –($C_1$-$C_6$ alkylene)aryl, or -($C_3$-$C_8$ cycloalkylene)(aryl); wherein each of the foregoing $R_2$ groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, and $C_1$-$C_6$ alkyl, wherein one of said one to three substituents can further be selected from bromo, iodo, $C_1$-$C_6$ alkoxy, -OH, -O-CO-($C_1$-$C_6$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -S($C_1$-$C_5$ alkyl), -S(O)($C_1$-$C_8$ alkyl), -S(O)$_2$($C_1$-$C_6$ alkyl), $S^+$($C_1$-$C_6$ alkyl)($C_1$-$C_2$ alkyl)$I^-$, CN, and $NO_2$; and wherein the $C_1$-$C_{12}$ alkyl, -($C_1$-$C_6$ alkylene), -($C_5$-$C_8$ cycloalkyl), -($C_5$-$C_8$ cycloalkylene), and -($C_5$-$C_8$ heterocycloalkyl) moieties of $R_2$ may optionally independently include from one to three double or triple bonds; and wherein each heterocycloalkyl group of $R_2$ includes from one to three heteromoieties selected from oxygen, $S(O)_m$, nitrogen, and $NR_{12}$;

or when $R_1$ and $R_2$ are as in –NHCH$R_1R_2$, -OCH$R_1R_2$, -SCH$R_1R_2$, –CH$R_1R_2$ or -N$R_1R_2$, $R_1$ and $R_2$ of B may form a saturated 5- to 8-membered ring which may optionally include one or two double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen, $S(O)_m$, nitrogen or $NR_{12}$; and which ring can optionally be substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, $C_1$-$C_4$ alkyl, fluoro, chloro, bromo, iodo, $CF_3$, -O-($C_1$-$C_4$ alkyl), -O-CO-($C_1$-$C_4$ alkyl), -O-CO-NH($C_1$-$C_4$ alkyl), -O-CO-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -NH($C_1$-$C_4$ alkyl), -N($C_1$-$C_2$ alkyl)($C_1$-$C_4$ alkyl), -S($C_1$-$C_4$ alkyl), -N($C_1$-$C_4$ alkyl)CO($C_1$-$C_4$ alkyl), -NHCO($C_1$-$C_4$ alkyl),-COO($C_1$-$C_4$ alkyl), -CONH($C_1$-$C_4$ alkyl), -CON($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), CN, $NO_2$, -OSO$_2$($C_1$-$C_4$ alkyl), -SO($C_1$-$C_4$ alkyl), and –SO$_2$($C_1$-$C_4$ alkyl), wherein one of said one to three substituents can further be selected from phenyl;

$R_3$ is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, $OCF_3$, $NH_2$, NH($C_1$-$C_2$ alkyl), N($CH_3$)$_2$, -NHCO$CF_3$, -NHC$H_2CF_3$, S(O)$_m$($C_1$-$C_4$ alkyl), $CONH_2$, -CONHC$H_3$, CON($CH_3$)$_2$, -$CF_3$, or C$H_2$OC$H_3$;

$R_4$ is hydrogen, $C_1$-$C_4$ alkyl, $C_3$-$C_5$ cycloalkyl, -($C_1$-$C_4$ alkylene)($C_3$-$C_5$ cycloalkyl), -($C_3$-$C_5$ cycloalkylene)($C_3$-$C_5$ cycloalkyl), cyano, fluoro, chloro, bromo, iodo, -$OR_{24}$, $C_1$-$C_6$ alkoxy, -O-($C_3$-$C_5$ cycloalkyl), -O-($C_1$-$C_4$ alkylene)($C_3$-$C_5$ cycloalkyl), -O-($C_3$-$C_5$ cycloalkylene)($C_3$-$C_5$ cycloalkyl), -C$H_2$SC(S)O($C_1$-$C_4$ alkyl), -C$H_2$O$CF_3$, $CF_3$, amino, nitro, -N$R_{24}R_{25}$, -($C_1$-$C_4$ alkylene)-$OR_{24}$, -($C_1$-$C_4$ alkylene)Cl, -($C_1$-$C_4$ alkylene)N$R_{24}R_{25}$, -NHC$OR_{24}$, -NHCON$R_{24}R_{25}$, -C=N$OR_{24}$, -NHN$R_{24}R_{25}$, -S(O)$_m$$R_{24}$, -C(O)$R_{24}$, -OC(O)$R_{24}$, -C(O)CN, -C(O)N$R_{24}R_{25}$, -C(O)NHN$R_{24}R_{25}$, and –C$OOR_{24}$, wherein the alkyl and alkylene groups of $R_4$ may optionally independently include one or two double or triple

bonds and may optionally independently be substituted with one or two substituents $R_{10}$ independently selected from hydroxy, amino, -$NHCOCH_3$, -$NHCOCH_2Cl$, -$NH(C_1$-$C_2$ alkyl), -$N(C_1$-$C_2$ alkyl)($C_1$-$C_2$ alkyl), -$COO(C_1$-$C_4$ alkyl), -COOH, -$CO(C_1$-$C_4$ alkyl), $C_1$-$C_6$ alkoxy, $C_1$-$C_3$ thioalkyl, cyano and nitro, and with one to four substituents independently selected from fluoro and chloro;

$R_5$ is aryl or heteroaryl and is substituted with from one to four substituents $R_{27}$ independently selected from halo, $C_1$-$C_{10}$ alkyl, -($C_1$-$C_4$ alkylene)($C_3$-$C_8$ cycloalkyl), -($C_1$-$C_4$ alkylene)($C_4$-$C_8$ heterocycloalkyl), -($C_3$-$C_8$ cycloalkyl), -($C_4$-$C_8$ heterocycloalkyl), -($C_3$-$C_8$ cycloalkylene)($C_3$-$C_8$ cycloalkyl), -($C_3$-$C_8$ cycloalkylene)($C_4$-$C_8$ heterocycloalkyl), $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ haloalkoxy, nitro, cyano, -$NR_{24}R_{25}$, -$NR_{24}COR_{25}$, -$NR_{24}CO_2R_{26}$, -$COR_{24}$, -$OR_{25}$, -$CONR_{24}R_{25}$, -$CO(NOR_{22})R_{23}$, -$CO_2R_{25}$, -$C{=}N(OR_{22})R_{23}$, and –$S(O)_mR_{23}$; wherein said $C_1$-$C_{10}$ alkyl, $C_3$-$C_8$ cycloalkyl, ($C_1$-$C_4$ alkylene), ($C_3$-$C_8$ cycloalkyl), ($C_3$-$C_8$ cycloalkylene), and ($C_4$-$C_8$ heterocycloalkyl) groups can be optionally substituted with from one to three substituents independently selected form $C_1$-$C_4$ alkyl, $C_3$-$C_8$ cycloalkyl, ($C_1$-$C_4$ alkylene)($C_3$-$C_8$ cycloalkyl), -($C_3$-$C_8$ cycloalkylene)($C_3$-$C_8$ cycloalkyl), $C_1$-$C_4$ haloalkyl, hydroxy, $C_1$-$C_6$ alkoxy, nitro halo, cyano, -$NR_{24}R_{25}$, -$NR_{24}COR_{25}$, $NR_{24}CO_2R_{26}$, -$COR_{24}$, -$OR_{25}$, -$CONR_{24}R_{25}$, $CO_2R_{26}$, -$CO(NOR_{22})R_{25}$, and –$S(O)_mR_{23}$; and wherein two adjacent substituents of the $R_5$ group can optionally form a 5-7 membered ring, saturated or unsaturated, fused to $R^5$, which ring optionally can include one, two, or three heterologous members independently selected from O, $S(O)_m$, and N, but not any –S-S-, -O-O-, -S-O-, or –N-S- bonds, and which ring is optionally substituted with $C_1$-$C_4$ alkyl, $C_3$-$C_8$ cycloalkyl, -($C_1$-$C_4$ alkylene)($C_3$-$C_8$ cycloalkyl), -($C_3$-$C_8$ cyloalkylene)($C_3$-$C_8$ cycloalkyl), $C_1$-$C_4$ haloalkyl, nitro, halo, cyano –$NR_{24}R_{25}$, $NR_{24}COR_{25}$, $NR_{24}CO_2R_{26}$, -$COR_{24}$, -$OR_{25}$, -$CONR_{24}R_{25}$, $CO_2R_{26}$, -$CO(NOR_{26})R_{25}$, or –$S(O)_mR_{23}$; wherein one of said one to four optional substituents $R_{27}$ can further be selected from -$SO_2NH(C_1$-$C_4$ alkyl), -$SO_2NH(C_1$-$C_4$ alkylene)($C_3$-$C_8$ cycloalkyl), -$SO_2NH(C_3$-$C_8$ cycloalkyl), -$SO_2NH(C_3$-$C_8$ cycloalkylene)($C_3$-$C_8$ cycloalkyl), -$SO_2N(C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), -$SO_2NH_2$, -$NHSO_2(C_1$-$C_4$ alkyl), -$NHSO_2(C_3$-$C_8$ cycloalkyl), -$NHSO_2(C_1$-$C_4$ alkylene)($C_3$-$C_8$ cycloalkyl), and -$NHSO_2(C_3$-$C_8$ cycloalkylene)($C_3$-$C_8$ cycloalkyl); and wherein the alkyl, and alkylene groups of $R_5$ may independently optionally include one double or triple bond;

$R_7$ is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -$O(C_1$-$C_2$ alkyl), -O(cyclopropyl), -$COO(C_1$-$C_2$ alkyl), -$COO(C_3$-$C_8$ cycloalkyl), -$OCF_3$, $CF_3$, -$CH_2OH$, or $CH_2OCH_3$;

$R_{11}$ is hydrogen, hydroxy, fluoro, ethoxy, or methoxy;

$R_{12}$ is hydrogen or $C_1$-$C_4$ alkyl;

$R_{22}$ is independently at each occurrence selected from hydrogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ haloalkyl, $C_3$-$C_6$ alkenyl, $C_3$-$C_8$ alkynyl, $C_3$-$C_8$ cycloalkyl;

$R_{23}$ is independently at each occurrence selected from $C_1$-$C_4$ alkyl, $C_1$-$C_4$ haloalkyl, $C_2$-$C_8$ alkoxyalkyl, $C_3$-$C_8$ cycloalkyl, aryl, -($C_1$-$C_4$ alkylene)aryl, piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine, and thiomorpholine;

$R_{24}$ and $R_{25}$ are independently at each occurrence selected from hydrogen, -$C_1$-$C_4$ alkyl, $C_1$-

$C_4$ haloalkyl, ~~especially $CF_3$, $CHF_2$, $CF_2CF_3$, or $CH_2CF_3$,~~ -($C_1$-$C_4$ alkylene)OH, -($C_1$-$C_4$ alkylene)-O-($C_1$-$C_4$ alkyl), -($C_1$-$C_4$ alkylene)-O-($C_3$-$C_5$ cycloalkyl), $C_3$-$C_8$ cycloalkyl, -($C_1$-$C_4$ alkylene)($C_3$-$C_8$ cycloalkyl), -($C_3$-$C_8$ cycloalkylene)($C_3$-$C_8$ cycloalkyl), -$C_4$-$C_8$ heterocycloalkyl, -($C_1$-$C_4$ alkylene)($C_4$-$C_8$ heterocycloalkyl), -($C_3$-$C_8$ cycloalkylene)($C_4$-$C_8$ heterocycloalkyl), aryl, and -($C_1$-$C_4$ alkylene)(aryl), wherein the -$C_4$-$C_8$ heterocycloalkyl groups can each independently optionally be substituted with aryl, $CH_2$-aryl, or $C_1$-$C_4$ alkyl, and can optionally include one or two double or triple bonds; or, when $R_{24}$ and $R_{25}$ are as $NR_{24}R_{25}$, -$C(O)NR_{24}R_{25}$, -($C_1$-$C_4$ alkylene)$NR_{24}R_{25}$, or -$NHCONR_{24}R_{25}$, then $NR_{24}R_{25}$ may further optionally form a 4 to 8 membered heterocyclic ring optionally including one or two further hetero members independently selected from $S(O)_m$, oxygen, nitrogen, and $NR_{12}$, and optionally including from one to three double bonds;

$R_{26}$ is independently at each occurrence selected from $C_1$-$C_4$ alkyl, $C_1$-$C_4$ haloalkyl, $C_3$-$C_8$ cycloalkyl, -($C_1$-$C_4$ alkylene)($C_3$-$C_8$ cycloalkyl), -($C_3$-$C_8$ cycloalkylene)($C_3$-$C_8$ cycloalkyl), aryl, and -($C_1$-$C_4$ alkylene)(aryl); and

wherein each m is independently zero, one, or two,

with the proviso that heterocycloalkyl groups of the compound of formula I do not include any –S-S-, -S-O-, -N-S-, or –O-O- bonds, and do not include more than two oxygen or $S(O)_m$ heterologous members.

2. (Original) A compound according to claim 1, wherein $R_4$ is -$NHCH_2CF_3$, -$CONHNH_2$, -$CONHNHCH_3$, –$OCF_3$, fluoro, -$OCHF_2$ , -$OCH_2$($C_3$-$C_5$ cycloalkyl), -O-($C_3$-$C_5$ cycloalkyl), -$SCH_2$($C_3$-$C_5$ cycloalkyl), -S($C_3$-$C_5$ cycloalkyl), –$OCH_3$, -$CH_3$, – $CH_2CH_3$, chloro, bromo, –$CF_3$, –$CH_2OH$, –$CH_2OCH_3$, -$CH_2OCF_3$, -$SCH_3$, –$S(O)CH_3$, –$S(O)_2CH_3$, –$C(O)CH_3$, –$NR_{24}R_{25}$, –$NO_2$, -$CH(OH)CH_3$, or –CN.

3. (Original) A compound according to claim 1, wherein $R_4$ is –$C(O)NR_{24}R_{25}$ or -$C(O)NHNR_{24}R_{25}$.

4. (Original) A compound according to claim 1, wherein $R_4$ is -($C_1$-$C_4$ alkylene)$NR_{24}R_{25}$.

5. (Original) A compound according to claim 1, wherein $R_4$ is –$COOCH_3$ or –$COOCH_2CH_3$.

6. (currently amended) A compound of formula I according to claim 1, wherein Z is O; B is –$NHCHR_1R_2$, wherein $R_1$ is -C(O)H, or -C(O)($C_1$-$C_6$ alkyl), ~~or -$C_3$-$C_6$ alkyl~~, wherein said $C_1$-$C_6$ alkyl is optionally substituted with from one to six fluoro atoms or one or two $R_8$ independently selected from –$C_1$-$C_4$ alkyl, hydroxy and –O-($C_1$-$C_6$ alkyl), and wherein $R_2$ is –$C_1$-$C_{12}$ alkyl optionally including from one to three double or triple bonds and optionally substituted with from one three substituents selected from fluoro and $C_1$-$C_6$ alkyl; $R_5$ is phenyl, pyridyl or pyrimidyl, substituted with two or three $R_{27}$ groups selected from halo, -($C_1$-$C_4$ haloalkyl), -$C(O)R_{24}$, -$OR_{25}$, -$C(O)NR_{24}R_{25}$, and $C_1$-$C_{10}$ alkyl which is

optionally substituted with one to three substituents selected from hydroxy, $C_1$-$C_6$ alkoxy, and –$NR_{24}R_{25}$; and $R_4$ is -$C(O)NR_{24}R_{25}$.

7. (currently Amended) A compound of formula I according to claim 1, wherein Z is O; B is -$NHCHR_1R_2$, wherein $R_1$ of –$NHCHR_1R_2$ is -C(O)H, or -C(O)($C_1$-$C_6$ alkyl), ~~or $C_1$-$C_6$ alkyl~~, wherein said $C_1$-$C_6$ alkyl is optionally substituted with from one to six fluoro atoms or one or two $R_8$ independently selected from –$C_1$-$C_4$ alkyl, hydroxy and –O-($C_1$-$C_6$ alkyl), and wherein $R_2$ of –$NHCHR_1R_2$ is –$C_1$-$C_{12}$ alkyl optionally including from one to three double or triple bonds and optionally substituted with from one three substituents selected from fluoro and $C_1$-$C_6$ alkyl; $R_5$ is phenyl, pyridyl or pyrimidyl, substituted with two or three $R_{27}$ groups selected from halo, -($C_1$-$C_4$ haloalkyl), -$C(O)R_{24}$, -$OR_{25}$, -$C(O)NR_{24}R_{25}$, and $C_1$-$C_{10}$ alkyl which is optionally substituted with one to three substituents selected from hydroxy, $C_1$-$C_6$ alkoxy, and –$NR_{24}R_{25}$; and $R_4$ is –$NR_1R_2$, wherein $R_1$ of –$NR_1R_2$ is $C_1$-$C_6$ alkyl, $C_3$-$C_8$ cycloalkyl, or -($C_1$-$C_6$ alkylene)($C_3$-$C_8$ cycloalkyl), and $R_2$ of –$NR_1R_2$ is $C_1$-$C_{12}$ alkyl optionally including from one to three double or triple bonds and optionally substituted with from one three fluoro atoms.

8. (currently Amended) A compound ~~according to claim 1~~ selected from:

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6,N-dimethyl-nicotinamide;

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6,N-dimethyl-nicotinamide;

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6-methyl-nicotinamide;

2-(4-bromo-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinamide;

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-methoxy-propylamino)-6-methyl-nicotinamide;

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-methoxy-propylamino)-6,N-dimethyl-nicotinamide;

2-(4-chloro-2-trifluoromethoxy-phenoxy)-4-(1-ethyl–propylamino)-6-methyl-nicotinamide;

2-(4-chloro-2-trifluoromethoxy-phenoxy)-4-(1-ethyl-propylamino)-6-N-dimethyl-nicotinamide;

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1S,2R-1-ethyl-2-methoxy-propylamino)-6,N-dimethyl-nicotinamide;

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1S,2S-1-ethyl-2-methoxy-propylamino)-6,N-dimethyl-nicotinamide;

2-(4-bromo-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinonitrile;

4-[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzamide;

2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(1-methylsulfanylmethyl-propylamino)-nicotinic acid methyl ester;

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester;

2-(4-bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinonitrile;

2-(4-chloro-2-trifluoromethoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid methyl ester; and

2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(tetrahydro-furan-3-ylamino)-nicotinic acid methyl ester;

~~[2-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethyl-propyl)-amine;~~

and pharmaceutically acceptable salts thereof.

9. (Currently Amended) A pharmaceutical composition for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF; or (b) a disorder or condition selected from ~~inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies~~; generalized anxiety disorder; panic; phobias, ~~including social phobia, agoraphobia, and specific phobias~~; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception ~~such as fibromyalgia~~; mood disorders ~~such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression~~; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; irritable bowel syndrome; spastic colon; post operative ileus; ~~ulcer;~~ diarrhea; stress-induced fever; ~~neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease~~; gastrointestinal diseases; hemorrhagic stress; chemical dependencies or addictions, ~~including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs~~; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; ~~head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, for example cerebral hippocampal ischemia; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions, including~~ porcine stress syndrome, ~~bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human animal interaction stress in dogs; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis;~~ hypertension; tachycardia; and congestive heart failure; ~~osteoporosis and premature birth in a mammal or bird~~, comprising an amount of a compound according to claim 1 that is effective in the treatment of such disorder or condition, and a pharmaceutically acceptable carrier.

10. (Currently Amended) A method for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF, or (b) a disorder or condition selected from ~~inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies~~; generalized anxiety disorder; panic; phobias, ~~including social phobia, agoraphobia, and specific phobias~~; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception ~~such as fibromyalgia~~; mood disorders ~~such as depression, including major depression, single episode depression, recurrent depression, child abuse~~

~~induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression~~; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; irritable bowel syndrome; spastic colon; post operative ileus; ~~ulcer~~; diarrhea; stress-induced fever; ~~neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease~~; gastrointestinal diseases; hemorrhagic stress; chemical dependencies or addictions, ~~including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs~~; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; ~~head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, for example cerebral hippocampal ischemia; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions, including~~ porcine stress syndrome~~, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human animal interaction stress in dogs; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis;~~ hypertension; tachycardia; and congestive heart failure; ~~osteoporosis and premature birth in a mammal or bird~~, comprising administering to a subject in need of said treatment an amount of a compound according to claim 1, that is effective in treating such disorder or condition.

11. (Original) A method of treating a condition comprising administering a compound of claim 1 in an amount effective to treat said condition, wherein said condition is selected from the group consisting of:

a) abnormal circadian rhythm;

b) depression, further wherein a second compound for treating depression is administered, said second compound for treating depression having an onset of action that is delayed with respect to that of said CRF antagonist; and

c) emesis.

12. (Original) The method of claim 11 wherein the condition is abnormal circadian rhythm, and the compound is combined with a second compound useful for treating a sleep disorder.

13. (Original) The method of claim 12, wherein said second compound is selected from the group consisting of tachykinin antagonists, agonists for GABA brain receptors, metalonergic compounds, GABA brain receptor agonists, 5HT2 receptor antagonists, and D4 receptor binding.

14. (currently amended) The method of claim 11 wherein said condition is depression, and wherein said second compound having delayed action for treating depression is selected from the group consisting of selective serotonin reuptake inhibitors, tricyclic antidepressants, norepinephrine uptake inhibitors, lithium, bupropion, ~~sertraline, fluoxetine,~~ trazodone, and a tricyclic antidepressant ~~selected from the group consisting of imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotiline, and carbamazepine~~, and

pharmaceutically acceptable salts and esters of the above-recited compounds.

15. (Original) The method claim 11 wherein said condition is emesis, further comprising administering a second compound for treating emesis.

16. (Original) The method of claim 15 wherein said second compound for treating emesis is selected from the group consisting of tachykinin antagonists, 5HT3 antagonists, GABA agonists, and substance P inhibitors.

17. (Previously Amended) A pharmaceutical composition for treating a condition comprising a compound of claim 1 in an amount effective to treat said condition and a pharmaceutically acceptable carrier, wherein said condition is selected from the group consisting of:

a) abnormal circadian rhythm;

b) depression, further wherein a second compound for treating depression is administered, said second compound for treating depression having an onset of action that is delayed with respect to that of said compound of claim 1; and

c) emesis.

18. (Original) A pharmaceutical composition according to claim 17, wherein the condition is abnormal circadian rhythm, and the compound is combined with a second compound useful for treating a sleep disorder.

19. (Original) A pharmaceutical composition according to claim 18, wherein said second compound is selected from the group consisting of tachykinin antagonists, agonists for GABA brain receptors, metalonergic compounds, GABA brain receptor agonists, $5HT_2$ receptor antagonists, and D4 receptor binding .

20. (currently amended) A pharmaceutical composition according to claim 17 wherein said condition is depression, and wherein said second compound having delayed action for treating depression is selected from the group consisting of selective serotonin reuptake inhibitors, tricyclic antidepressants, norepinephrine uptake inhibitors, lithium, bupropion, ~~sertraline, fluoxetine,~~ trazodone, and a tricyclic antidepressant ~~selected from the group consisting of imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotiline, and carbamazepine~~, and pharmaceutically acceptable salts and esters of the above-recited compounds.

21. (Original) A pharmaceutical composition according to claim 17 wherein said condition is emesis, further comprising administering a second compound for treating emesis.

22. (Original) A pharmaceutical composition according to claim 21 wherein said second compound for treating emesis is selected from the group consisting of tachykinin antagonists, 5HT3 antagonists, GABA agonists, and substance P inhibitors.

23. (New) The pharmaceutical composition of claim 9, wherein the disorder or condition is a phobia selected from the group consisting of including social phobia, agoraphobia, and specific phobias.

24. (New) The pharmaceutical composition of claim 9, wherein the disorder or condition is a pain perception, wherein the pain perception is fibromyalgia.

25. (New) The pharmaceutical composition of claim 9, wherein the disorder or condition is depression.

26. (New) The pharmaceutical composition of claim 25, wherein the depression is selected from the group consisting of major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression.

27. (New) The pharmaceutical composition of claim 9, wherein the chemical dependency or addictions is selected from the group consisting of dependencies or addictions to alcohol, cocaine, heroin, and benzodiazapines.

28. (New) The method of claim 10, wherein the disorder or condition is a phobia selected from the group consisting of including social phobia, agoraphobia, and specific phobias.

29. (New) The method of claim 10, wherein the disorder or condition is a pain perception, wherein the pain perception is fibromyalgia.

30. (New) The method of claim 10, wherein the disorder or condition is depression.

31. (New) The method of claim 10, wherein the depression is selected from the group consisting of major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression.

32. (New) The method of claim 10, wherein the chemical dependency or addictions is selected from the group consisting of dependencies or addictions to alcohol, cocaine, heroin, and benzodiazapines.

33. (New) The method of claim 14, wherein the selective serotonin reuptake inhibitor is sertraline or fluoxetine or pharmaceutically acceptable salts and esters thereof and the tricyclic antidepressant is selected from the group consisting of imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotiline, and carbamazepine and pharmaceutically acceptable salts and esters thereof.

34. (New) The pharmaceutical composition of claim 20, wherein the selective serotonin reuptake inhibitor is sertraline or fluoxetine or pharmaceutically acceptable salts and esters thereof and the tricyclic antidepressant is selected from the group consisting of Imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotiline, and carbamazepine and pharmaceutically acceptable salts and esters thereof.